IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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PATENT & TRADEMARK OFFICE
JUN 06 2000
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In re patent application	
No.	08/634,039
Applicant:	Denis P. Snider
Title:	METHODS AND COMPOSITIONS CONTAINING ANTIGENS HAVING A TARGETING MOIETY SPECIFIC FOR ANTIGEN PRESENTING CELLS FOR INTRANASAL IMMUNIZATION
Filed:	April 17, 1996
Group No.	1644
Examiner:	F. VanderVegt

June 5, 2000

BY COURIER

The Commissioner of Patents
and Trademarks,
Washington, D.C. 20231,
U.S.A.

Dear Sir:

This communication is in response to the Office Action of September 14, 1999.

The courtesy of the Examiner in granting an Interview on this application to the applicant's representative, Mr. Michael Stewart, and to Mr. Reza Yacoob, a member of the Patents Department of the Assignee, Connaught Laboratories Limited, is much appreciated. It is believed that the Interview was useful in focussing the issues for further consideration. The Interview Summary Record reflects the substance of the discussion at the Interview.

In the Final Action, the Examiner recognized Applicant's intention to submit a new Declaration by Mark R. McDermott, correctly stating that he does not consider himself to be an inventor of the claimed invention, contrary to the impression given by the unsigned Declaration originally submitted with the

application. Accordingly, submitted herewith is a Declaration under 37 CFR 1.148(a) now correctly stating that he is not an inventor.

It is recognized that the file wrapper and filing receipt reflect that Denis Snider is the sole inventor. However, it is considered desirable to correct the record, so as to explain the apparent discrepancy between the Declaration executed only by Denis Snider and the unsigned Declaration referring to three inventors.

Accordingly, submitted herewith is a combined Declaration and Power of Attorney newly executed by Denis Snider.

In the Final Action, the Examiner rejected claims 1 to 6 and 8 under 35 USC 103(a) as being unpatentable over Barber et al USP 4,950,480 or Barber et al USP 5,194,254, each in view of Wu et al.

Applicant's claims are directed to a method of generating an immune response to an antigen in a host by intranasal administration to the host of an antigen coupled to a targeting moiety specific for surface structures of antigen-presenting cells.

The Barber '480 and '254 patents describe a method of conferring protection against pathogenic organisms using monoclonal antibodies specific for membrane determinants expressed on mammalian antigen presenting cells as a targeting moiety, which are coupled to antigens derived from pathogenic organisms. As the Examiner states in the Final Action:

> "The '480 patent and the '254 patent do not teach intranasal administration or a heterobifunctional linking molecule."

It is considered surprising that a strong immune response to the antigen can be evoked by intranasal administration. Applicants consider that the success in eliciting a good immune response to the antigen by parenteral administration, as described in the cited Barber references, is not in any way predictive of the results obtained by applicant by intranasal administration.

The Examiner seeks to make up for the deficiencies of the Barber et al references by reliance on Wu et al. As stated in the Final Action:

> "Wu et al teaches the intranasal administration of *Streptococcus mutans* surface protein antigen I/II (AgI/II) coupled to cholera toxin B subunit (CRB)... AgI/II and CTB are coupled through a

heterobifunctional linking molecule."

The basis of the Examiner's rejection is contained in the Final Action:

> "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to be motivated to combine the teachings of the '480 or '254 patents concerning anti-APC mAb-antigen conjugates with the teachings of Wu et al concerning intranasal administration of antigen to elicit a protective response to pathogenic organisms."

Much of the discussion at the Interview centred on this rejection. The remarks contained herein and the literature cited in support thereof compliment and supplement the remarks made to the Examiner at the Interview.

It is true that the prior art Barber et al patents teach that conjugates of antibody and antigen, given in solution by intravenous or other parenteral instillation, evoke antigen-specific antibody response, and immunologic memory, as discussed above. Those skilled in the art agree that the mechanism concerns the ability of the antibody conjugate to freely diffuse throughout the body and bind specifically to antigen presenting cells (APC), thereby initiating immune response, as described, for example, in Fossum, et al, Semin. Immunol. 4, 275-283 (1992), Carayanniotis et al, Nature 327, 59-61 (1987) and Skea et al, Vaccine 11, 994-1002 (1993). These literature references and others discussed herein are listed on the enclosed PTO-1449, along with the art already made of record in this case, and copies of the newly-cited references only are enclosed herewith. The binding and response are dependent on the antibody specificity. The antibody must be able to reach the tissues where the APC reside. The Barber et al patents provided ready access for the antibody to those tissues because they always used parenteral injections.

However, it is submitted that it is not obvious that monoclonal antibodies or antibody-antigen conjugates applied to the epithelial surfaces of the nasal passages (or other external body surfaces) would be able to reach circulation or even the underlying lymphoid tissues of the epithelium in substantial quantity. Those skilled in the art would understand that the epithelial layers of the nasal passages have tight junctions and that large macromolecules (such as antibodies or conjugates) do not pass through the epithelium, except with very poor efficiency. In

fact, immunization of mouse nasal passages with CTB as, described by Wu et al, works only poorly, unless large quantities of CTB are used or small amounts of cholera toxin are also available, allowing increased permeability of the epithelium to antigens, as described, for example, in Tamura et al, Vaccine 12, 419-426 (1994) and Tamura et al, Microbiol, Immunol., 32, 1145-1161 (1988), as is also the case in intestinal epithelium, as described, for example, in Lycke et al, Scand. J. Immunol. 33, 691-698 (1991).

The antibodies used in the applicant's experimentation have specificity for class II MHC molecules, expressed by APC. These class II MHC molecules are only poorly expressed by non-inflamed nasal epithelial cells of young rodents, as described, for example, in Hameleers et al, Cell Tissue Res. 256, 431-438 (2000), such as the mice that the applicant immunized. In addition, there is no evidence that MHC class II molecules are expressed on the external membrane (apical surface) of rodent nasal epithelial cells. Available immunohistochemistry suggests only intracellular localization of class II MHC in the rodent nasal epithelium and those published results cannot define apical expression, as described, for example, in Koornstra et al, Acta Otolaryngol. 113, 660-667 (1993).

Thus, applicant had no reason to believe that the antibody conjugate would bind specifically to the epithelium or be taken up by the epithelium based on the anti-class II MHC specificity. The only likelihood was that small amounts of the conjugate would get past the epithelium and interact with APC below the epithelium or in the draining lymph nodes.

Having regard thereto, it is submitted that one skilled in the art would have no reasonable expectation of success in being able to obtain a protective immune response by intranasal administration of the Barber et al conjugates. It is submitted that it is a surprising result that such a high degree of induction of antigen-specific immunity was achieved in applicant's experimentation by application to the external surfaces of the nasal passages of mice.

As noted above, the work of Wu et al concerns protein conjugates between antigen and cholera toxin B subunit (CTB) protein. Unlike the antibody conjugates utilized herein, the CTB conjugates do not bind specifically to APC. They are not a specific targeting moiety that will only bind to CTB. Indeed, the specificity

of CTB (the targeting moiety) is for the GM1-ganglioside, a glycolipid molecule that is found on almost all mammalian cells, as described, for example, in van Heyningen, Science 183, 656-657 (1974) and King et al, J. Infect. Dis. 127, 639-647 (1973). Further, GM1-ganglioside is displayed on the apical surface of all epithelial cells. In fact, the GM1-gaglioside specificity of CTB is its primary function, allowing binding of the complete cholera entertoxin to the intestinal epithelium. This is widely known and understood information on the function of CTB, as described, for example, in Middlebrook, Microbiol. Rev. 48, 199-221 (1984), Spangler, Microbiol. Rev. 56, 622-647 (1992), and Snider, Crit. Rev. Immunol. 15, 317-348 (1995). Thus, the conjugates of Wu et al. would bind directly to the apical epithelium of nasal epithelium, and this mechanism is likely the primary reason why those CTB conjugates provide immune stimulation. Even if the CTB conjugates get past the epithelium, their mode of action would not be specifically to act on APC, because they would bind many other types of cells, including lymphocytes, as described, for example, in Holinger, Imunol, Comm 5,737-756 (1976).

It is apparent, therefore, that the mechanism of functionality of the Wu et al CTB conjugates would, in no manner, predict that the antigen-antibody conjugates of Barber et al would act in a manner similar to the CTB conjugates. CTB conjugates have a completely different targeting mechanism from the antigen-antibody conjugates that primarily involve binding to the apical surface of epithelial cells, in contrast to the antibody antigen conjugates, which do not bind to the apical surface of epithelial cells. It is submitted that immune responses generated by CTB conjugates, in the nasal mucosa, as described by Wu et al, do not predict similar responses by antibody-antigen conjugates and certainly not by a mechanism that specifically targets antigen presenting cells, as described by Barber et al.

Accordingly, it is submitted that claims 1 to 6 and 8 are patentable over the combination of Barber et al US Patent No. 4,950,480 or Barber et al, US Patent No. 5,194,254, each in view of Wu et al, and hence the rejection thereof under 35 USC 103(a) as being unpatentable over the prior art, should be withdrawn.

In the Final Action, the Examiner rejected claim 7 under 35 USC 103(a) as being unpatentable over Barber et al US Patent No. 4,950,480 or Barber et al US Patent No. 5,194,254, each in view of Wu et al and further in view of

Dempsey et al and ATCC Catalogue of Cell Lines and Hybridomas. Claim 7 is dependent on claim 1.

The relevance of the combination of the Barber et al patents each with Wu et al, has been discussed above. It is submitted that the additionally cited secondary references do not make up the deficiencies of this combination.

As the Examiner points out, Dempsey et al teaches conjugation of antigen to C3d and ATCC catalogue offers for sale the hybridoma which produces the anti-human C3d receptor (CD21) Mab THB-5. However, the Dempsey et al conjugate is administered to mice intraperitoneally and hence is no more relevant to the patentability of claim 7 than the Barber et al patents and to the patentability of claim 1, on which claim 7 ultimately depends.

In the Final Office Action, the Examiner comments that:

> ". . . the antibody-antigen conjugate taught by Dempsey et al can easily be substituted for the conjugate taught by the '480 and '254 patents and used intranasally based upon the aforementioned combination of the '480 or the '254 patent with Wu et al."

As discussed in detail above, there is a complete lack of motivation to use the Barber et al conjugates for intranasal administration. Whether the conjugates of Dempsey et al are substituted for those of Barber et al does not alter the lack of motivation.

Accordingly, it is submitted that claim 7 is patentable over the combination of Barber et al, US Patent No. 4,950,480 or Barber et al US Patent No. 5,194,254, each in view of Wu et at and further in view of Dempsey et al and ATCC Catalogue, and hence the rejection thereof under 35 USC 103(a) as being unpatentable over the applied art, should be withdrawn.

In the Final Action, the Examiner rejected claim 9 under 35 USC 103(a) as being unpatentable over Barber et al, US Patent No. 4,950,480 or Barber et al US Patent No. 5,194,284, each in view of Wu et al, and further in view of Babington, US Patent No. 4,228,795. Claim 9 claims the combination of an aerosol spray dispenser with the Barber et al antibody antigen conjugate to enable the conjugate to be nasally administered.

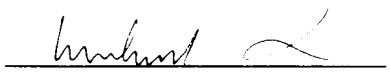
The basic combination of references is discussed above, along with the defects thereof. The Babington reference is relied on for a teaching of a nebulizer which can be used to aerosolize medicaments for nasal inhalation and not for any teaching which would serve to remedy the defects of the primary combination of references and as discussed in detail above.

In particular, the basic combination of prior art lacks any motivation to package the antibody-antigen conjugate of the Barber et al patents in an aerosol spray dispenser, since the prior art lacks any motivation to effect intranasal administration of the antibody antigen conjugates of Barber et al, for the reasons discussed in detail above.

Accordingly, it is submitted that claim 9 is patentable over the applied combination of Barber et al US Patent No. 4,950,480 or Barber et la US Patent No. 5,194,254, each in view of Wu et al, and further in view of Babington et al, and hence the rejection thereof under 35 USC 103(a) as being unpatentable over the applied prior art, should be withdrawn.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,



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